B_2 is selected from the group consisting of a C_1-C_{19} alkylamido, a C_1-C_{19} alkyl, a C_2-C_{19} alkenyl, a C_2-C_{19} alkynyl, a C_1-C_{19} hydroxyalkyl, a C_1-C_{19} alkyl carbamoyl, a C_1-C_{19} alkylcarbonyl, and an aralkyl, any of which can be further substituted with one or more substituents, which can be the same or different, selected from the group consisting of a nitro, a halo, an azido, a hydroxy, an amido and an amino group; and

X is a polar moiety selected from the group consisting of an amino acid, a polypeptide and a protein;

or a pharmaceutically acceptable salt of said compound.

83. (Amended) The method of claim 81, wherein

B_2 is selected from the group consisting of a C_1-C_7 alkylamido, a C_1-C_7 alkyl, a C_2-C_7 alkenyl, a C_2-C_7 alkynyl, a C_1-C_7 hydroxyalkyl, a C_1-C_7 alkyl carbamoyl, a C_1-C_7 alkylcarbonyl, and an aralkyl, any of which can be further substituted with one or more substituents, which can be the same or different, selected from the group consisting of a nitro, a halo, an azido, a hydroxy, an amido, and an amino group.

REMARKS

The Present Invention

The present invention pertains to a water-soluble compound, a composition thereof, a method of treating cancer with the water-soluble compound, and a method of preparing a water-soluble compound.

The Pending Claims

Claims 63, 65, 66, 68-70, 72, 73, 75-77, 79-81, 83-87, 90 and 91 are currently pending. Claims 63, 65, 66, 68-70 and 72 are directed towards the water-soluble compound. Claims 73, 75 and 76 are directed towards the composition comprising the water-soluble compound. Claims 77, 79 and 80 are directed towards the method of treating cancer with the water-soluble compound. Finally, claims 81, 83-87, 90 and 91 are directed towards the method of preparing a water-soluble compound.

Amendments to the Specification and Claims

The specification has been amended to correct obvious typographical errors with respect to two references that were cited correctly in the Information Disclosure Statement filed April 18, 2001, as References AJ and AK.

The claims have been amended to point out more particularly and claim more distinctly the present invention. In particular, claims 64, 67, 71, 74, 78, 82, 88 and 89 have been canceled. Claims 92-106 have been canceled as directed towards non-elected

subject matter. Claim 63 has been amended to include the elements of claims 64, 67 and 71. Similarly, claim 81 has been amended to include the elements of claims 82, 88 and 89. In view of claim cancellations, the dependencies of claims 65, 68 and 83 have been amended. Claims 77, 79 and 80 have been amended to recite that the cancer expresses heat shock protein 90 (Hsp90), as supported by the specification at, for example, page 2, lines 5-12. No new matter has been added by way of these amendments. The precise changes to the specification and claims and the pending claims, as amended, are set forth on attachments hereto.

Summary of the Office Action

The Office has maintained the prior restriction requirement; however, the Office has indicated that Groups I and II (i.e., claims 63-91) will be examined together. Claims 63-91 have been rejected as being drawn to an improper Markush group. Claims 63-91 have been rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite. Finally, the Office has rejected claims 77-80 under 35 U.S.C. § 112, first paragraph, as allegedly non-enabled. Applicants note that the Office Action indicates the rejection of claims 61 and 62; however, these claims were canceled in a preliminary amendment filed January 17, 2001. Reconsideration of the pending claims is respectfully requested.

Discussion of the Improper Markush Rejection

According to the Office, claims 63-91 lack unity of invention, since substituent A is defined in such a way that the core compound keeps changing. The claims have been amended to recite that substituent A is a water-insoluble drug selected from the group consisting of a macrolide and an ansamacrolide. In view of the amendment, the rejection is believed to be moot.

Discussion of the Section 112, second paragraph, Rejection

The Office has rejected claims 63-91 as allegedly indefinite, since the spacer moiety (i.e., B_1 and B_2) and the polar moiety (i.e., X) are not specified. The claims have been amended to recite more specific embodiments of B_1, B_2 and X. In view of the amendments, the rejection is believed to be moot.

Discussion of the Section 112, first paragraph, Rejection

Claims 77-80 (claim 78 has been canceled) have been rejected as allegedly non-enabled. According to the Office, the specification does not provide enablement of cancer generally. The Office further alleges that nearly all anticancer drugs are effective against only a limited group of related cancers. This rejection is traversed for the reasons set forth below.

The claims have been amended to recite that the cancer to be treated expresses Hsp90. Therefore, Applicants are not claiming that all cancers are treated with the compounds of the present invention, only those cancers in which Hsp90 is expressed. It is generally recognized within the art that macrolides and ansamacrolides, such as, for example, geldanamycin and derivatives thereof, are effective inhibitors of Hsp90. See, for example, Neckers, L., *Trends Mol. Med.*, 2002, 8(4 Suppl): S55-61; Blagosklonny, M. V., *Leukemia*, 2002, 16(4): 455-462; Workman, P. et al., *Expert Opin. Biol. Ther.*, 2002, 2(1): 3-24; and Munster, P. N. et al., *Cancer Res.*, 2001, 61(7): 2945-2952 (abstracts enclosed). A compound of the present invention can bind to Hsp90, thereby precluding Hsp90 from binding to other signaling proteins that are necessary for the survival of cancer cells. In the absence of binding to Hsp90, these signaling proteins are destabilized and eventually degrade so that the cancer growth is inhibited.

The specification provides teachings to those of ordinary skill in the art how to make and use the present invention. In particular, Applicants point out that Examples 3 and 4 of the instant specification describe the efficacy of water-soluble compounds of the present invention to treat cancers that express Hsp90. In addition, water-soluble compounds are described in the specification at, for example, page 7, line 20, to page 16, line 21. Chemical synthesis of the water-soluble compounds is described in the specification at, for example, page 32, line 7, to page 35, line 3. Compositions are described in the specification at, for example, page 23, line 25, to page 27, line 10. Suitable doses are described in the specification at, for example, page 31, line 17, to page 32, line 5. Formulations of the water-soluble compounds are described in the specification at, for example, page 27, line 11, to page 29, line 22, and includes modes of administration, carriers, and concentrations. Therefore, no undue experimentation would be required for one of ordinary skill in the art to practice the method of the present invention, as defined by claims 77, 79 and 80. Accordingly, claims 77, 79 and 80 are enabled by the specification, and this rejection should be withdrawn.

Conclusion

The application is considered to be in good and proper form for allowance, and the Examiner is respectfully requested to pass this application to issue. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned attorney.

Respectfully submitted,

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Date: December 6, 2002

CERTIFICATE OF MAILING

I hereby certify that this AMENDMENT AND RESPONSE TO OFFICE ACTION (along with any documents referred to as being attached or enclosed) is being deposited with the United States Postal Service on the date shown below with sufficient postage as first class mail in an envelope addressed to: Commissioner of Patents and Trademarks, Washington, D.C. 20231.

Date: Dec. 6, 2002 Kathleen D. Grant